Biologic Therapy and the Risk of Malignancy in Psoriasis

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ABSTRACT
Biologic agents are currently regarded as a highly efficacious systemic treatment for moderate to severe psoriasis. However, their use in patients with a history of malignancy or an increased risk of cancer is not recommended. The current recommendations are based on several case reports and observational studies, as well as data from randomized, controlled trials, associating these medications with tumorigenic properties. Furthermore, some reports describe malignancies arising de novo in patients using biologic agents. Psoriasis patients are at an increased risk of lymphoproliferative diseases and nonmelanoma skin cancers because of the inflammatory nature of the disease. A blockade of tumor necrosis factor-alpha (TNF-α) reduces inflammation but also may enhance tumor proliferation. Trials have not shown a significant increase in the risk of malignancy, with the exceptions of lymphoma and nonmelanoma skin cancers, with the use of TNF blockers. However, any risk may be unacceptable in a patient with a history or elevated risk of cancer. Ustekinumab acts on a different inflammatory pathway and may have a different profile regarding the risk of malignancy. A comprehensive review of the literature shows some consensus that relative contraindications are active malignancies and malignancies within the past 5 years. There is debate about nonmelanoma skin cancers and melanoma, but it seems prudent to use biologics more cautiously in a patient with a history of aggressive skin cancer, a high risk of recurrent skin cancer, or a history of extreme ultraviolet exposure. Additionally, certain combinations of immunosuppressive therapies, such as purine analogs, with biologics may lead to unacceptable risks of malignancy. Some subgroups, such as patients with chronic obstructive pulmonary disease, are already predisposed to lung cancer because of a significant smoking history; these patients require closer monitoring during biologic therapy. As the biologics are in use longer for psoriasis, more data on the long-term safety of these therapeutics will be available.

INTRODUCTION
Psoriasis is a common chronic inflammatory disease of the skin and joints that can manifest at any age. About 2% of the U.S. general population suffers from psoriasis, and many of these patients require systemic modalities of treatment to control the disease.1 Specifically, moderate to severe psoriasis is an indication for the most recent additions to the standard systemic treatments: the biologic agents.2 By targeting specific steps implicated in the pathogenesis of psoriasis, biologic agents are able to modify the immune response.

Several of the biologic agents are highly efficacious treatments for psoriasis; however, data regarding long-term potential systemic toxicities are limited. In particular, there is concern for an increased

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risk of malignancies and infections with the use of biologic medications secondary to the effects of immunosuppression.3,4 Psoriasis patients are likely susceptible to lymphoproliferative malignancies and nonmelanoma skin cancers because of the inflammatory nature of psoriasis, past immunosuppressive therapies, or ultraviolet (UV) exposure.5 As biologic therapies are increasingly used in dermatologic practice, attention to the current literature regarding an associated risk of malignancy is of considerable importance in the management of patients with psoriasis.

Epidemiologic studies have established a connection between autoimmune inflammatory diseases—such as rheumatoid arthritis (RA) and psoriasis—and malignancy.6,7 According to a review by the U.S. Food and Drug Administration (FDA), RA patients may have a twofold increased risk of developing lymphoma.8 Furthermore, the severity of the disease has been correlated with increased lymphoma risk. Baecklund and colleagues reported a risk increase from fivefold in moderate RA to 20-fold in severe RA.9

Similarly, psoriasis has been associated with an increased risk of lymphoproliferative malignancies correlated with disease severity.10-12 The strongest link was demonstrated with severe psoriasis and Hodgkin’s lymphoma (adjusted RR, 3.18; 95% CI, 1.01-9.97) and cutaneous T-cell lymphoma (adjusted RR, 10.75; 95% CI, 3.89-29.76).12

Patients with RA may have an intrinsic risk for nonmelanoma skin cancer. A large cohort study, relying on self-reported semiannual questionnaires, compared the risk of nonmelanoma skin cancer in RA patients with that of osteoarthritis patients.13 The hazard ratio (HR) in the RA population for the development of nonmelanoma skin cancer was increased to 1.19 (P = .042). An increased risk of nonmelanoma skin cancer in psoriasis patients has likewise been suggested.10,13

METHODS
Reports in the literature were reviewed regarding biologic therapies and risk of malignancy. Articles were retrieved via PubMed using a two- or three-word combination of the following terms: cancer, malignancy, tumor necrosis factor antagonist, infliximab, etanercept, adalimumab, alefacept, efalizumab, ustekinumab, rheumatoid arthritis, and psoriasis. The first few searches done were of malignancy plus one of the biologic medications. Each search produced about 50 articles, most of which were related to our investigation. More general search terms such as psoriasis and malignancy led to many more articles; however, most of these were irrelevant. Articles deemed irrelevant included any article without reference to biologic therapy, psoriasis, or another indication of biologic treatment in relation to malignancy risk.

RESULTS
Tumor Necrosis Factor-α Antagonists and Malignancy
The association between malignancy and anti-TNF-α agents (i.e., infliximab, adalimumab, and etanercept) has been an issue of uncertainty in the literature. Generally, immunosuppression is a risk factor for the development of malignancies.3 There is a predilection for the development of tumors, specifically of the skin and lymphoid tissue, in transplant patients who are receiving potent immunosuppressant medications.14 Notably, the most concern for patients receiving anti-TNF therapy has also been for lymphoma and nonmelanoma skin cancers. In addition to the general immunosuppressive concerns, the role of TNF-α in tumor surveillance via apoptosis has raised concern for the possibility of anti-TNF therapy further predisposing individuals to tumor growth. As discussed earlier, the risk of malignancy with biologic agents is confounded by the independent risk of lymphoproliferative malignancies and cutaneous cancers associated with the FDA-approved indications for TNF blockers.5,9,10,12,13

Because of a lack of power, many controlled trials have been inconclusive in establishing a greater risk of malignancy in RA and psoriasis patients using TNF-α inhibitors.15-17 Limitations of existing randomized, controlled trials include short-term duration and insufficient numbers of subjects enrolled to detect cancers that may arise after many years of treatment or appear after cessation of therapy. Observational studies relying on RA registries have attempted to overcome these limitations; however, the findings have been inconsistent and contradictory. A current review of the available data on TNF antagonist therapy in FDA-indicated medical conditions—RA, Crohn’s disease, ankylosing spondylitis (AS), and psoriasis—and the association to malignancy may clarify what has been and what has yet to be
established about the oncogenic potential of these biologic medications.

**Lymphoma and TNF Blockers in Rheumatoid Arthritis and Psoriasis**

The immunosuppressive effect of anti-TNF agents in psoriasis patients may increase the risk of lymphoproliferative diseases and, perhaps specifically, virally mediated B-cell lymphomas. As early as 2002, Brown et al. identified 26 FDA-reported lymphomas arising shortly after receiving the anti-TNF agents etanercept and infliximab. Based on the short period between treatment and development of lymphoma, the study raised concern for the immunosuppressive role of TNF blockers in accelerating the growth of latent lymphomas. Moreover, in one patient taking etanercept and one taking infliximab, the lymphomas resolved on discontinuation of the TNF blocker.

**Lymphoma and TNF blockers in randomized, controlled trials**

The association between lymphoma and anti-TNF therapy is recognized and is the source of concern. Package inserts of all three TNF blockers state that more reported cases of lymphoma have been observed in patients treated with TNF antagonists compared with control patients in randomized, controlled trials. Based on several clinical trials, a 2003 FDA advisory committee reported increased standardized incidence ratios (SIR) noted for lymphoma in RA patients of 3.47 (95% CI, 1.6-6.6) for etanercept, 6.35 (95% CI, 1.7-16.3) for infliximab, and 5.42 (95% CI, 2.6-10.0) for adalimumab. Although the data suggest an increased lymphoma risk with use of TNF blockers, the advisory committee noted that it is unclear whether this increased risk is due to the expected increased risk generally observed in RA patients. Additionally, patients enrolled in such clinical trials and treated with TNF antagonists may represent a population that already has a greater predisposition for the development of malignancy because of their greater disease severity.

Additional data from randomized, controlled trials were provided by a recent review on the safety of adalimumab across six indications. Twenty-six global trials and a total of 19,401 patients receiving adalimumab were included. The authors noted that only in the RA trials was there a statistically significant increased lymphoma risk compared with the general population. The calculated SIR for the increased risk, 2.98 (95% CI, 1.89-4.47), may potentially be accounted for by the intrinsic lymphoma risk linked to RA.

In addition, clinical trials of infliximab have examined the risk for lymphoma in treated patients. For trials across all indications, five cases of lymphoma of 4,996 patient-years were noted. Compared with the general population, an SIR of 4.55 (95% CI, 1.48-10.61) was calculated. However, the calculated SIR included patients with highly active Crohn's disease, plaque psoriasis, and RA, all of whom may be at increased risk for lymphoma irrespective of biologic use. The observed threefold lymphoma risk in RA patients only (SIR, 3.21; 95% CI, 0.39-11.60) is comparable to the reported lymphoproliferative risk associated with the RA population.

Short-term psoriasis clinical trials with infliximab have not demonstrated an increased risk of lymphomas compared with the general population. No cases of lymphoma were reported in an analysis of three psoriasis clinical trials for a maximum duration of 1 year. Long-term studies specific to psoriasis are needed to evaluate fully any rare adverse events, such as malignancy, that may be detected only over a more extended period.

Lack of power of clinical trials may be overcome by meta-analyses of several trials. A systemic review of nine trials, comprising 3,316 RA patients, was conducted by Bongartz and associates to evaluate the overall malignancy risk of etanercept. A nonstatistically significant higher incidence of malignancies was found, excluding nonmelanoma skin cancers, in the etanercept-treated group compared with the placebo group (HR, 1.86; 95% CI, 0.62-5.59). Despite pooling data from several trials, the authors note that the study was underpowered to demonstrate an increased risk.

Bongartz et al. conducted a controversial large meta-analysis on the risk of infections and malignancies in RA patients treated with infliximab or adalimumab. Nine randomized clinical trials were included of up to 54 weeks’ duration. Twenty-nine malignancies were observed in the 3,493 treated patients compared with three cases.
in the 1,512 control patients. A threefold risk for all malignancies (OR, 3.3; 95% CI, 1.2-9.1) was calculated for patients treated with anti-TNF monoclonal antibodies compared with those in the control group. Additionally, a subgroup analysis was performed comparing trials using high- and low-dose anti-TNF therapy. A significant difference was found between these groups. The calculated ORs for high-dose and low-dose therapy compared with placebo were 4.3 (95% CI, 1.6-11.8) and 1.4 (95% CI, 0.3-5.7), respectively. Another finding of the study was no accumulation of malignancies with trials of longer study duration. Based on the short lag time between the initiation of anti-TNF therapy and the detection of malignancies, the authors suggest a role for TNF inhibitors in promoting the growth of subclinical malignancies rather than the induction of malignancies de novo.24

Numerous shortcomings of this study have been cited.25,26 Specifically, the rate of malignancy in the studied control arm was much lower than expected in the general RA population.25 One proposed explanation for this discrepancy is that the higher dropout rate of control patients in the included trials may have led to a shorter duration for malignancy detection.26 The threefold increased risk in TNF inhibitor–treated patients should be adjusted for the lower-than-expected risk reported in the control patients. Another inherent flaw with the study is the lack of standardization for severity of disease. Several reports demonstrated an increased risk of lymphoma in RA patients with increasing activity of disease. A recent observational study investigating time trends of reported malignancies with TNF antagonist therapy found a higher rate of lymphoma in the treated group during the years 1998-2001 versus later years.27 The stated possibility was that patients with more severe disease were given TNF antagonists during the time when treatment was recently initiated. If more severely afflicted patients were in the treated group, this would account for the reported higher risk of malignancy demonstrated in the meta-analysis by Bogartz et al.24 Another limitation of the study is the inclusion of trials ranging from 3 months to 1 year. A meta-analysis of results from studies with widely spread duration assumes that there is no change in the incidence of malignancy from 3 months to 1 year; yet the length of time associated with the development of malignancies with the use of TNF inhibitors is not yet known.26 Lastly, trials of etanercept were not included in the meta-analysis. The authors explained the exclusion of etanercept as being due to the concurrent inhibition of lympho toxin-α, which may play a role in tumor growth, in addition to the antagonism of TNF.24 Because etanercept is an anti-TNF receptor protein, it has different biologic activity compared with infliximab and adalimumab, anti-TNF monoclonal antibodies. However, etanercept is a popular TNF antagonist in clinical practice, and the FDA has requested its inclusion in a meta-analysis such as this one.28

Attempts to clarify the results of the meta-analysis by Bogartz et al. have led to the addition of randomized clinical trials published subsequent to the study.28 Adjusting the data based on the PREMIER trial, Costenbader et al. found a decrease in the originally reported OR for all malignancies in treated patients compared with control patients (OR, 2.02; 95% CI, 0.95-4.29).28 Bogartz et al. included two additional studies, the PREMIER study and the study by Westhovens et al., in a follow-up letter that also reported a decreased OR for all malignancies in RA patients treated with adalimumab or infliximab (OR, 2.4; 95% CI, 1.2-4.8).28 However, the authors still noted an association between dose and risk of malignancy in the stratified analysis. An OR of 4.5 (95% CI, 1.6-12.8) was documented for high-dose anti-TNF therapy versus placebo compared with an OR of 2.6 (95% CI, 1.2-5.6) for low-dose versus placebo patients.28

A recent meta-analysis by Dommasch et al. pooled results from 20 randomized, controlled trials investigating the rate of infection and malignancy in psoriasis or psoriatic arthritis patients treated with TNF antagonists.29 The study did not demonstrate an increased risk of malignancy in the treated psoriasis patients compared with the control group with an incidence rate ratio of 0.99 (95% CI, 0.51-1.90). Perhaps, unlike the RA population, psoriasis patients are less frequently taking multiple immunosuppressants while undergoing biologic therapy. The authors suggest the possibility that the increased malignancy risk demonstrated in RA patients receiving biologic agents by Bogartz et al. may correlate to the role of combination immunosuppressant therapy. Methotrexate was concomitantly being taken by 77.4% of RA patients in the study by Bogartz et al. Conversely, 17 of the 20 studies included in the meta-analysis by Dommasch
et al. excluded psoriasis patients receiving any other immunosuppressant therapy while using biologic agents. It would seem that monotherapy with biologic agents is likely safer than combination therapies with two immunosuppressive agents.

**Lymphoma and TNF blockers in observational studies**

Long-term registries comprising thousands of RA and psoriasis patients taking TNF antagonists have been reviewed to clarify a possible increased risk of lymphoma. The results among various studies have been inconclusive and even contradictory at times. Additionally, extrapolating data from RA registries for psoriasis patients may not be valid.

The Swedish Biologics Register, comprising RA patients receiving anti-TNF therapy across eight rheumatologic centers, was used in three reports regarding lymphoma risk. The first published study compared the incidence of cancer between a subgroup of the registry from 1997 to 2002 with a cohort of RA patients from the same region. Although the overall incidence of cancer was the same for the two cohorts, the lymphoma risk was increased by an RR of 4.9 (95% CI, 0.9-27.9) in the anti-TNF treated group. Five lymphoma cases were reported of the 757 biologic patients versus two observed cases of the 800 control patients. However, the severity of disease was not controlled for, and there is a likely possibility that patients with more active disease, specifically in the earlier years of the study, were treated with biologic agents. Therefore, it is difficult to conclude whether the increased risk is related to severity of disease or to the use of a TNF antagonist. In another investigation using a subgroup from the registry between 1999 and 2003, the relative risk of lymphoma in the biologic cohort was not increased compared with the control group (RR, 1.1; 95% CI, 0.6-2.1). The discrepancy between the two studies is not clear but is likely due to the use of biologics agents in more severely affected patients in the earlier years.

Recently, Askling et al. attempted to classify more completely the trends in the development of lymphoma in patients with RA by relying on data from the Swedish Biologics Register from the years 1998 to 2006. By further stratifying data, they were able to support their past study conclusion that there was no statistically significant increased risk of lymphoma in patients using TNF-antagonist therapy (RR = 1.35). There was, however, a higher incidence of malignancy in RA patients treated in the earlier years (1998-2001) of biologic therapy compared with the later years (2004-2006). The relationship between disease severity and use of TNF inhibitors in the earlier years may explain this finding. Another important conclusion of the study was that there was no increase in lymphoma risk with accumulated time on anti-TNF agents, nor was there any temporal association with the development of malignancies.

Similarly, relying on the National Data Bank for Rheumatic Diseases, Wolfe et al. initially reported a slight, nonstatistically significant increase in lymphoma risk in RA patients treated with TNF-antagonists but subsequently observed no increased risk in an extended study. Between 1999 and 2002, 14 cases of lymphoma of 8,614 anti-TNF-treated patients were reported, and a relative risk of 1.3 was calculated. In the extended study, including registry patients between 1998 and 2006, an OR of 1.0 (95% CI, 0.6-1.8) was observed for the risk of lymphoma of the 10,833 anti-TNF treated patients compared with the 8,758 patients either not treated or treated with methotrexate (MTX) only. Because MTX users are used as the comparison group, it should be noted that an OR of 1.0 in this study does not exclude the possibility that both MTX and biologic therapy increase the risk of malignancy to the same degree in this patient population. The study suggests that there is no increased risk of lymphoma with the use of TNF antagonists compared with a more standard therapy, MTX. Additional findings included no increased risk with the concurrent use of MTX and anti-TNF agents (OR, 1.1; 95% CI, 0.6-2.0). Another study, using two U.S. Medicare databases (1994-2004) and one Canadian administrative database (1996-2003), analyzed data from 1,152 RA patients using etanercept, infliximab, or anakinra and 7,306 RA patients taking MTX. The pooled adjusted HRs in patients treated with biologic therapy compared with MTX users were 1.11 (95% CI, 0.51-2.37) for lymphoproliferative cancers and 1.37 (95% CI, 0.71-2.65) for hematopoietic malignancies. The authors proposed that because MTX and TNF blockers are systemic medications used to treat moderate to severe RA, comparing these two groups may reduce the confounding variable of disease severity that has been proposed in other studies.
The results of observational studies are reassuring. Observational studies may be useful in providing additional information, such as demographic data, that may serve to guide clinical decisions regarding TNF-antagonist therapy. Factors such as increasing age, male gender, and severity of disease seem to predispose patients to cancer in some observational studies. Close follow-up may be even more important in patients with such demographics to detect malignancies as soon as possible.

**TNF Blockers and lymphomas of specific concern**

**Hepatosplenic T-cell lymphoma and TNF inhibitors**

Postmarketing reports of hepatosplenic T-cell lymphomas after the use of infliximab and adalimumab have been alarming because of the rare and aggressive nature of this malignancy. Six of the eight adolescent patients developing hepatosplenic T-cell lymphomas while receiving infliximab died within a year. In general, hepatosplenic T-cell lymphoma has been associated with iatrogenic immunosuppression in a quarter of reported cases. Therefore, it is not surprising that all patients who developed it while taking TNF antagonists were concurrently being treated with a purine analog, either azathioprine (AZA) or 6-mercaptopurine (6-MP) for inflammatory bowel disease (IBD), Crohn’s disease, or ulcerative colitis. Such medications are not typically used to treat psoriasis, and no reports of hepatosplenic T-cell lymphomas have been reported in psoriasis patients. Furthermore, the type of inflammation and the variant of T cells present in Crohn’s disease likely differ from the pathogenesis leading to psoriasis. Accordingly, the risk of hepatosplenic T-cell lymphomas does not likely apply to psoriasis patients using only TNF antagonists.

**Cutaneous T-cell lymphoma and TNF inhibitors**

Several cases of cutaneous T-cell lymphoma have been reported in psoriasis patients receiving TNF inhibitors. Adams et al. reported a male patient with psoriatic arthritis treated with etanercept and a female patient with Crohn’s disease using infliximab who developed aggressive CD30+ cutaneous T-cell lymphomas. Rapid progression of the disease led to the death of both patients.

Use of potent immunosuppressive medications while on TNF-antagonist therapy may heighten the risk of cutaneous T-cell lymphomas. Mahe et al. reported an erythrodermic psoriasis patient treated with infliximab for 3 months who developed CD30+ cutaneous T-cell lymphoma with lymph node involvement 3 weeks after reintroducing cyclosporine. The malignancy regressed within 1 month of cessation of treatment. Cyclosporine has been independently associated with cutaneous T-cell lymphoma in psoriasis patients and thus may heighten risk when added to TNF-antagonist therapy.

**Summary—TNF-α antagonists and lymphoma**

There is evidence that psoriasis patients, in general, are at an increased risk for lymphoproliferative malignancies because of the inflammatory nature of the disease and past immunosuppressive therapies. However, it has yet to be established that TNF antagonists further elevate such a risk. Regardless, a thorough history eliciting past or active lymphomas and a physical examination should be performed before treatment and routinely for the duration of therapy. The use of anti-TNF therapy in patients at high risk for lymphoma or who have a history of lymphoma is cautioned against in all three TNF blocker packaging inserts and should be considered only after a careful risk-benefit analysis (refer to Boxes 1, 2, and 3). Use of these medications in patients with existing lymphoma is not advised.

Because of the alarming case reports of hepatosplenic T-cell lymphoma in adolescents with IBD, it is not recommended for patients taking AZA or 6-MP to be given concurrent TNF blockers. Caution is warranted in patients with a history of use of purine analogs as well.

The use of immunosuppressive therapies, such as cyclosporine, may increase lymphoma risk in psoriasis patients. Development of cutaneous T-cell lymphoma in a patient treated with infliximab and cyclosporine warrants caution when considering such combination therapy.

**Nonlymphoma Malignancies and TNF Blockers**

Although most concern regarding the increased potential for cancer has been primarily centered around lymphoma, the actions of TNF inhibitors in tumor surveillance theoretically may also play a role in the more common solid cancers. In addition to several case reports of solid malignancies, there...
is evidence for an elevated risk of nonmelanoma skin cancer in psoriasis patients that may be further elevated by anti-TNF therapy. Nonetheless, the overall incidence of malignancies, excluding lymphoma and nonmelanoma skin cancer, has not been shown to occur at a higher frequency in RA or psoriasis patients treated with TNF antagonists than in the general population.

Nonlymphoma malignancies and TNF blockers in randomized clinical trials

Clinical trials examining the safety of infliximab have not demonstrated an increased risk for malignancies. Across several indications, 63 cases of malignancies of any kind were observed in the infliximab group of 10,242 person-years. Compared with the Surveillance, Epidemiology End Results (SEER), the calculated SIR of 1.04 (95% CI, 0.80-1.33) suggested that the risk of infliximab-treated patients is similar to that of the general public. Interestingly, this risk was higher than that observed in the placebo group. However, the observed SIR of 0.84 (95% CI, 0.38-1.59) in the placebo group was lower than expected in the general population. The significance of these data is unclear but does not support an increased risk of malignancy in infliximab-treated patients compared with the general population. In psoriasis clinical trials with infliximab, excluding nonmelanoma skin cancer, the rate of malignancies was not significantly higher than that of the general population.

The use of adalimumab in several randomized clinical trials was similarly not associated with a significantly greater incidence of malignancies besides lymphoma and nonmelanoma skin cancers.

Box 1. Infliximab (REMICADE) Safety Information Pertaining to Malignancies

- Unusual cancers have been reported in children and teenage patients taking tumor necrosis factor (TNF) blockers. A rare form of fatal lymphoma has occurred mostly in teenage or young adult males with Crohn’s disease or ulcerative colitis who were taking REMICADE and azathioprine or 6-mercaptopurine. For children and adults taking TNF blockers, including REMICADE, the chances of getting lymphoma or other cancers may increase.
- You should let your doctor know if you have or ever had any of the following: any type of cancer or a risk factor for developing cancer, for example, chronic obstructive pulmonary disease (COPD), or if you have had phototherapy for psoriasis.
- The following serious (sometimes fatal) side effects have been reported in people taking REMICADE. You should tell your doctor right away if you have any of these signs: lymphoma or any other cancers in adults and children.

Box 2. Adalimumab (HUMIRA) Safety Information Pertaining to Malignancies

- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, of which HUMIRA is a member (See Warnings and Precautions). Post- marketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including HUMIRA. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases have occurred in patients with Crohn’s disease or ulcerative colitis, and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of hepatosplenic T-cell lymphoma is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants.
- For children and adults taking TNF blockers, including HUMIRA, the chances of getting cancer may increase.
- There have been cases of unusual cancers in children, teenagers, and young adults using TNF blockers.
- People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
- If you use TNF blockers, including HUMIRA, your chance of getting two types of skin cancer may increase (basal cell cancer and squamous cell cancer of the skin). These types of cancer are generally not life-threatening if treated. Tell your doctor if you have a bump or open sore that does not heal.
- Some people receiving TNF blockers including HUMIRA developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn’s disease or ulcerative colitis with another medicine called IMURAN (azathioprine) or PURINETHOL (6-mercaptopurine).

Box 3. Etanercept (Enbrel) Safety Information Pertaining to Malignancies

- There have been cases of unusual cancers in children and teenage patients who started using TNF-blocking agents at less than 18 years of age.
- For children, teenagers, and adults taking TNF-blocker medicines, including Enbrel, the chances of getting lymphoma or other cancers may increase.
- People with rheumatoid arthritis or psoriasis, especially those with very active disease, may be more likely to get lymphoma.

The SIR for malignancy from the six trials analyzed, including RA and PS patients, was 0.83 (95% CI, 0.72-0.96).15

Nonlymphoma malignancies and TNF blockers in observational studies

Many of the same observational studies that analyzed lymphoma risk in RA patients receiving biologic therapy noted no increase in incidence of overall malignancies in the studied RA population. Geborek
et al. reported an SIR for overall cancers of 1.1 (95% CI, 0.6-1.8) in treated RA patients compared with an SIR of 1.4 (95% CI, 1.1-1.8) in placebo patients. Similarly, Wolfe et al. observed an SIR of 1.0 (1.0-1.1) for overall malignancies in biologic-treated RA patients. Skin cancers were the only malignancies associated with increased risk in RA patients using TNF inhibitors (nonmelanoma skin cancer: OR, 1.5; 95% CI, 1.2-1.8; and melanoma: OR, 2.3; 95% CI, 0.9-5.4).

Askling et al. conducted an observational cohort study to determine specifically the risk of solid cancers in RA patients. The Swedish registry was used for the three cohorts, 1990-2003. The risk of solid cancers in RA patients treated with TNF inhibitors was similar to that reported for both the prevalent and incident control cohorts. Based on 67 malignancies observed in the 4,160 TNF inhibitor–treated RA patients, the SIR was calculated as 0.9 (95% CI, 0.7-1.2). Certain malignancies found to be increased in both RA patients and anti-TNF–treated RA patients compared with the general population were nonmelanoma skin cancers and smoking-related cancers (cancer of respiratory tract, urinary bladder, and kidney cancer). The authors mentioned that the risk of breast cancers and colorectal cancers may be less than expected in RA patients secondary to the protective function of nonsteroidal anti-inflammatory drugs, which are routinely used in the treatment of RA. No significant differences in site-specific risks were noted between the general RA population and those treated with biologic agents. Based on this study, it is difficult to extrapolate any additional risk of malignancy in psoriasis patients treated with TNF-antagonist treatment.

TNF blockers and concerns for specific non-lymphoma malignancies

Skin cancer and TNF inhibitors

The risk of nonmelanoma skin cancer is greater in psoriasis patients than in the general public. The increased risk may be at least partially explained by past treatment modalities used for psoriasis. Past potent immunosuppressive therapy and phototherapy with psoralen and ultraviolet A (PUVA) have been determined to increase risk of skin cancer. Specifically, common medications used in psoriasis—cyclosporine and MTX—are two immunosuppressant agents that have been associated with an increased risk of skin cancer; however, it is unclear whether this predilection persists after discontinuation of these treatments. Other recognized therapies that increase the risk of skin cancer include a history of Grenz ray therapy or arsenic use. Also of note, psoriasis is associated with a 1:1 ratio of cutaneous basal cell carcinoma to squamous cell carcinoma (SCC) compared with the 4:1 ratio found in the general public. Likely, the increased risk of SCC is based on the prevalence of sun exposure and the use of PUVA in psoriasis patients and immunosuppressive therapies such as cyclosporine and MTX.

The increased risk of nonmelanoma skin cancer in psoriasis patients may be further heightened by anti TNF-therapy. There have been multiple reports of cutaneous SCC developing in patients shortly after initiation of anti-TNF therapy. After removal of the offending drug, the regression of such malignancies witnessed in case reports may implicate TNF inhibitors in permitting the growth of subclinical malignancies. Ly et al. documented the occurrence of multiple SCCs and keratoacantomas (KAs) on the lower legs of a male patient with severe psoriasis 10 weeks following etanercept treatment. After discontinuation of the drug, the KAs regressed. The occurrence of SCCs in patients treated with etanercept has also been reported in RA patients. Smith et al. noted the short duration of 2 to 4 months between etanercept therapy and the development of SCC in seven RA patients. The authors suggest that the clinically evident actinic damage in the observed patients may support the existence of ultraviolet radiation-induced subclinical tumors before treatment. Furthermore, no new SCCs were seen after the cessation of treatment. Two case reports have documented the development of penile SCC in two psoriasis patients after 2 months and 34 months of etanercept. Both patients were human papillomavirus negative and had a previous history of systemic medications and PUVA therapy. The case of penile SCC presented by Comte and colleagues was particularly alarming because the disease progressed rapidly and led to the death of the patient.

Although the case reports merit some concern, a retrospective cohort study analyzing data from a clinical trial’s database and postmarketing database found no increased incidence of SCC in RA patients.
using etanercept compared with the general population. Interestingly, the development of the malignancies reported in the clinical trials' database and the postmarketing surveillance occurred 3 to 5 years after starting etanercept therapy compared with the shorter time frame observed in the case reports. The long lag time between etanercept and SCC would not support the role of anti-TNF therapy in accelerating subclinical malignancies. However, as the authors caution, the data cannot be extrapolated from a RA group to a psoriasis population. Furthermore, the regression of SCCs after withdrawal of anti-TNF treatment documented in some of the case reports warrants a high degree of suspicion.

The risk for the development of SCC might not be limited to etanercept therapy. A case report presented a RA patient with an extensive history of sun exposure and nonmelanoma skin cancer who developed multiple KAs and SCCs after 4 months of infliximab. Randomized clinical trials with infliximab supported a possible risk of nonmelanoma skin cancer. Seven of the 1,234 psoriasis patients treated with infliximab developed nonmelanoma skin cancer compared with none of the 334 placebo psoriasis patients.

Although most studies and cases have reported on nonmelanoma skin cancers, it should also be noted that recently cases of malignant melanoma in psoriasis patients treated with TNF antagonists have been reported. Fulchiero et al. presented two cases of recurrent malignant melanoma. After eight courses of etanercept, a female plaque psoriasis patient had an eruption of metastatic melanoma on the thigh, where she had previously had a primary melanoma. Similarly, a male RA patient was treated with adalimumab for 6 months before finding a malignant melanoma in an axillary node on the same side as his primary melanoma after 8 years of remission. Kowalzick and colleagues reported a male psoriasis patient who developed a malignant melanoma de novo after being consecutively treated with infliximab, adalimumab, and etanercept for a total of 30 months.

Lung cancer in COPD patients using TNF-α antagonists
There has been suggestion that TNF-α antagonists may increase the incidence of lung cancer in patients with preexisting chronic obstructive pulmonary disease (COPD). In a randomized 24-week controlled clinical trial of individuals with COPD and a heavy smoking history, more malignancies were reported in the infliximab-treated group (9 of 157) compared with the control group (1 of 77). Most of the reported malignancies were of the lung, head, and neck. One case of lymphoma was reported in an infliximab patient. A postmarketing analysis, based on a managed-care database, revealed a similar malignancy rate in the infliximab-treated COPD individuals compared with a COPD comparator group. With limited data, the significance of these reports is still unknown.

The risk of lung cancer in COPD patients treated with TNF blockers may be related to the disease state. It has been reported that RA may be associated with a higher rate of development of lung cancer. An observational study suggested an increase in the incidence of lung cancer in RA patients, both in patients treated with TNF-antagonists (SIR, 1.8; 95% CI, 0.9–3.3) and in control patients (SIR, 1.48; 95% CI, 1.33–1.65; and SIR, 2.4; 95% CI, 1.5–3.6) compared with the general population. No significant difference was observed between treated and control RA patients.

However, a recent case report argues for a more direct connection between TNF antagonist therapy and malignancy than merely a relation to the disease state. Lees et al. documented the regression of a non–small cell lung cancer in a 69-year-old woman with Crohn’s colitis who was initiated on MTX (continued to the present) and then infliximab; finally, she was maintained on adalimumab after discontinuing infliximab. After 2 years of adalimumab therapy, she was diagnosed with non–small cell lung cancer. Following withdrawal of the TNF blocker only, the patient underwent regression and then full remission of the lung cancer. Interestingly, a computed tomography–guided biopsy of the original tumor stained positive for type 1 and 2 TNF receptors. The authors note the implication of this finding on a carcinogenic role of TNF.

**Wegener’s and etanercept (with cyclophosphamide)**
A large trial of 180 patients with Wegener’s granulomatosis suggested that the use of etanercept with cyclophosphamide may increase the risk of solid cancers. All six (five noncutaneous solid tumors) of the observed solid malignancies occurred
in the 89 patients receiving both etanercept and cyclophosphamide. During the 6-month observation period, two of the three patients diagnosed with additional solid malignancies had been part of the etanercept group.

**Leukemia and TNF Inhibitors**

Several cases of acute or chronic leukemia have been reported in patients treated with etanercept or infliximab. Backland et al. were first to question the association between etanercept and acute myelogenous leukemia (AML) in a male patient with AS after 4 months of etanercept therapy. More recently, Bachmeyer and colleagues documented the development of AML in a man with severe psoriasis also 4 months after etanercept therapy. A third case of AML was reported in a male psoriatic arthritis patient after being treated with etanercept for 6 months. In this report, a chromosome analysis supported the link between biologic therapy and the development of leukemia by revealing a deletion on the chromosome 5p that is consistent with a drug-induced leukemia.

Case reports of leukemia in patients treated with infliximab have also been described. Alcain et al. noted the occurrence of acute lymphomatous leukemia in a man with Crohn’s disease after being treated with three infliximab 5 mg/kg infusions. Molecular biology demonstrated a \(\text{bcr/abl}\) fusion gene, which suggests a genetic predisposition to a hematologic malignancy. It cannot be established whether the inhibition of TNF-\(\alpha\) played a role in the progression of a subclinical malignancy. Subsequently, Broussais et al. reported chronic myelogenous leukemia in a woman with RA after a year and a half of infliximab treatment with concurrent MTX.

A recent pharmacovigilance report on TNF-\(\alpha\) inhibitors and leukemia searched a worldwide safety database for case reports of leukemia in connection to TNF-\(\alpha\) antagonist therapy. By November 2006, 12 cases of leukemia were reported in connection with adalimumab, 74 with infliximab, and 39 with etanercept. The authors noted in 103 of the 121 reports that TNF blockers were the only suspected drug recorded. The most common indications for therapy were RA and Crohn’s disease; exposure to the drug until diagnosis ranged from a few months to several years. The median age of the patients was 60 years old. Additionally, both acute and chronic leukemias occurred with no predilection for myeloid or lymphocytic leukemia.

**Summary—Nonlymphoma malignancies and TNF blockers**

With the exception of nonmelanoma skin cancers and lymphoma, no significant evidence has been found to show that the risk of overall malignancies is increased by the use of TNF antagonists. The risk of skin cancer, mainly nonmelanoma, in psoriasis may be elevated in patients treated with anti-TNF therapy. Patients with a history of sun exposure or nonmelanoma skin cancer or malignant melanoma should be followed closely when TNF-inhibitor treatment is initiated.

The risk of lung cancer or smoking-related tumors in COPD patients with psoriasis treated with biologics is unclear. The currently available data are based on RA patients, who may be predisposed to smoking-related cancers attributable to the disease state. Therefore, extrapolation of risk to psoriasis patients is difficult. Nonetheless, all patients with a heavy smoking history should be monitored closely for the development of smoking-related cancers.

A randomized, controlled trial and several case reports of patients with Wegener’s granulomatosis have led to concern for solid tumors with the use of etanercept and concurrent cyclophosphamide or other potent immunosuppressive therapy. The medication package insert recommends against this drug combination.

The significance of case reports of leukemia with anti-TNF therapy has not yet been elucidated. Until long-term control trials show support of these case reports, baseline and continuous complete blood counts would be prudent in patients being prescribed a TNF-antagonist. Guidelines have been proposed for this practice.

History of a malignancy is not a contraindication to TNF-\(\alpha\) antagonist therapy. A risk-benefit analysis should be done for individual patients as well as a thorough history of the malignancy and treatment. A guideline on the use of etanercept in psoriasis, published by a European panel of dermatologists, decided that a history of a malignancy in the past 5 years should be a contraindication to treatment.
Because of the limitations of long-term randomized, controlled studies and several published case reports of malignancies associated with biologic therapy, it is prudent to monitor closely all patients taking biologics. The recommendations of the authors are at minimum an annual total body check for skin cancers, basic bloodwork (complete blood cell count and comprehensive metabolic panel) every 2 months and close follow-up with a primary medical doctor. Therapy must be halted with the development of any concerning laboratory changes or clinical symptoms.

T-Cell Modulators and Malignancy

T-cell modulators have not received as much attention as the TNF-antagonists for their potential risk of malignancy. However, fewer data are available because these medications have not been previously used in diseases besides psoriasis. Nonetheless, efalizumab and alefacept are immunosuppressive agents that carry the potential to increase malignancies.

Efalizumab

On April 8, 2009, Genentech announced the withdrawal of efalizumab because of reported cases of progressive multifocal leukoencephalopathy (PML) in patients using efalizumab. As early as October 2008, a black-box label was added that warned about the possibility of a rare but alarming connection between efalizumab and PML. After three diagnosed cases and one suspected case, the risk-benefit ratio was deemed too high and efalizumab was officially taken off the market on June 2009.73 Before its withdrawal, a greater risk of malignancies had not been documented in psoriasis patients receiving efalizumab. A large meta-analysis pooling 14 clinical trials with 2,980 treated patients demonstrated a similar risk for all malignancies, including lymphoproliferative diseases and nonmelanoma skin cancers, in treated versus placebo psoriasis patients.75 Because the observation time was much shorter for the placebo patients, malignancy rates were obtained from two external psoriasis cohorts (United Healthcare and Saskatchewan Health) and also from SEER. Compared with these patients, the risk of NMSC was similarly increased in both efalizumab and placebo groups. The incidence rate of nonmelanoma skin cancer was 1.38 (95% CI, 0.96-1.92) in efalizumab patients, 1.08 (95% CI, 0.13-3.89) in placebo patients, and 0.39 (95% CI, 0.22-0.63) in both the United Healthcare and Saskatchewan Health databases. The authors noted the plausibility of increased reports of nonmelanoma skin cancer in the study population as a result of the increased surveillance while enrolled in clinical trials.51 The same meta-analysis reported a total of three lymphoproliferative malignancies observed exclusively in the efalizumab-treated group.51 Nonetheless, the incidence rate of 0.12 was comparable to that of the external cohorts (0.17 and 0.15).

Case reports have documented the development of lymphoproliferative diseases in psoriasis patients treated with efalizumab. Berthelot and associates described a male psoriasis patient developing an atypical CD8+ cutaneous T-cell lymphoma after 1 year of efalizumab therapy.69 Bommankanti et al. presented a case of Epstein-Barr virus–associated large B-cell lymphoma in a male psoriasis patient receiving efalizumab therapy.70 More recently, Hernandez et al. observed a male psoriasis patient who developed a cutaneous T-cell lymphoma 3 months after cessation of a 4-month trial of efalizumab therapy.71 In addition to the case reports of lymphoma, Morse et al. reported a case of cervical cancer in a patient with severe psoriasis after 27 months of efalizumab therapy.72

Summary—Efalizumab

No significantly increased risk of malignancy has been demonstrated in patients using efalizumab compared with the general psoriasis population. However, because of an increase in malignancies observed in the treated arm in clinical trials, the package insert currently lists malignancy as an adverse event.73 Case reports support the potential for an increased malignant risk resulting from the immunosuppressive effects of the medication.52,72 More long-term control studies will help clarify the significance of such reports. So far, open-label extension clinical trials have also not demonstrated an increased risk of malignancy in psoriasis patients treated with long-term efalizumab therapy.74

Alefacept

Alefacept has not been reported to increase the risk of malignancy in treated patients. However, during clinical trials, there were reports of malignancies occurring with treatment.74 Of 1,869 patients, 63
cancers arising during the treatment period were found in 43 patients. Most of the cancers were nonmelanoma skin cancers (46 cases in 27 patients), but 3 melanomas, 5 lymphomas, and 12 solid cancers were observed as well. In a controlled trial, the incidence of malignancy in the placebo group was 0.5% compared with 1.3% in the treated arm.75

The low incidence of malignancy in patients treated with alefacept has also been maintained in longer-term control trials.76,77 Investigating the safety of alefacept use for up to nine courses of therapy in a 5-year period, Goffe et al. performed an analysis that included 13 randomized, controlled clinical trials.78 The low malignancy rate in treated patients (0–4.8%) remained stable over the course of treatment. Consistent with the results of past clinical trials,43,45 most of the observed malignancies were nonmelanoma skin cancers (63%). There were also four lymphoproliferative malignancies and one case of mycosis fungoides. The rates of lymphoma, nonmelanoma skin cancer, and solid cancers were similar to those expected in psoriasis patients. Nonetheless, because of the association of potent immunosuppressive therapy and cancer, the packaging label has a warning about the oncogenic potential of the drug (see Box 4).75

Summary—Alefacept
There is no evidence that alefacept increases the risk of malignancy in the psoriasis population. However, if alefacept is initiated in patients with a history of malignancy, caution is advised.2,75

Interleukin-12 and Interleukin-23 Antagonists
Ustekinumab, the newest FDA-approved biologic agent for psoriasis, is a human monoclonal antibody against the p40 subunit shared by interleukin-12 (IL-12) and interleukin-23 (IL-23). Targeting cytokines other than the T-cell modulators or the TNF-α antagonists, ustekinumab may have a different safety profile from that of the other biologic agents on the market. Ustekinumab has not been associated with an increased risk of malignancy (see Box 5).

In two large phase III clinical trials including psoriasis patients, PHOENIX I and II, ustekinumab was not associated with an increase risk of malignancy.79,80 Other randomized, controlled trials for other indications, such as multiple sclerosis and Crohn’s disease,81,82 as well as a more recent study in psoriatic arthritis patients,83 have similarly found no association between ustekinumab and malignancy. A meta-analysis of three randomized, controlled trials with follow-up up to 28 weeks recently published by Tan et al. reported no increased incidence of cutaneous malignancies in the ustekinumab 45-mg or 90-mg groups compared with controls (RR 1.03, RR 0.61, respectively).84

Although perhaps the acceptable short-term safety profile of ustekinumab was demonstrated, the long-term safety data of up to 3 years including the rates of malignancy in treated psoriasis patients are only now in print. Pooling data from PHOENIX I and II and the ACCEPT trial, information from 3,117 psoriasis patients treated with ustekinumab could be analyzed. The rate of all malignancies in patients receiving either ustekinumab 45 mg or 90 mg, excluding nonmelanoma skin cancers, was 0.7 per 100 patients and 0.5 per 100 patients, respectively, over an average of 1.5 years. Comparing this to the rate per 100 placebo-treated patient-years, the rate in treated patient-years was not found to be increased.85

Screening Patients for Malignancy
When considering a patient for biologic therapy, a thorough history and physical should be performed to elicit past or current malignancies. Increased risk of malignancy or history of malignancy are not contraindications to treatment; however, caution is advised and a risk-benefit analysis should be performed in each case.1,16,19,20 One exception may be a history of lymphoma, given that some view this as an absolute contraindication to TNF-antagonist therapy.5 Nonetheless, there are case reports of biologic-treated patients with a history of lymphoma experiencing improvement of psoriasis without recurrence of malignancy.86 Such reports support individualized risk-benefit analysis for each patient.

According to published guidelines, biologic therapy is contraindicated in patients with an active or recent history of malignancy, with the exception of treated nonmelanoma skin cancers.1,5,87 It has not been specified how to define “recent”; however, one European panel of dermatologists proposed that a malignancy within 5 years is a contraindication.87
A thorough history of current and past medications must be elicited before initiating biologic therapy. The addition of a biologic agent to potent immunosuppressive treatments may increase the risk of malignancy. Specific medications that have raised concern in concurrent use with TNF blockers include AZA, 6-MP, cyclosporine, and cyclophosphamide. Past long-term use of immunosuppressive therapy may also increase risk of malignancy in psoriasis patients, so close follow-up would be prudent. Current use of such medications with TNF blockers is not advised unless the risk-benefit ratio indicates that its use is appropriate. Use of more than one TNF blocker is also not currently practiced for psoriasis treatment.

Additional considerations may be appropriate when determining the risk of malignancy in psoriasis patients initiating biologic therapy. Increased risk is likely linked to increasing disease severity and may be correlated to male gender, advancing age, or COPD.

Monitoring Patients Undergoing Biologic Therapy
Most guidelines note malignancy as a rare adverse event, and all suggest routine, periodic history and physical examinations in patients treated with biologics. Reevaluation of patients specifically to detect the development of symptoms suggestive of malignancy has also been recommended.

CONCLUSION
Psoriasis patients are at a higher risk than is the general public for the development of malignancies. The risk is elevated with increasing severity of the disease state. The association is strongest for lymphoproliferative malignancies and cutaneous malignancies. Many attribute the increased risk of malignancy in psoriasis to the intrinsic inflammatory disease process, past immunosuppressive therapies such as MTX and cyclosporine, and PUVA. Long-term control trials and observational studies in psoriasis patients are still needed to elucidate the risk of malignancy with use of biologic therapies.

In all FDA-approved biologic agents, case reports have been sufficiently alarming to lead to the addition of malignancy as a potential adverse event in the medication packaging. Nonetheless, such cases are of undetermined significance because it is difficult to prove the direct relation of drug to the development of malignancy.

Combining biologic agents with potent immunosuppressive therapies may lead to the development of certain malignancies. However, experimental studies have demonstrated no increased risk of malignancy associated with combination therapy of biologic agents and other systemic therapies for psoriasis. At this time, the practice of using two biologic therapies at the same time is not recommended in psoriasis treatment.

Screening before the initiation of biologic therapy and monitoring for the development of malignancies while in treatment are important considerations in the management of psoriasis. For patients reporting new symptoms that are suggestive of malignancy, suspicion of lymphoma, or indicating other malignancies should be considered in the differential diagnosis. Routine surveillance is necessary for the development of skin cancer in psoriasis patients on biologic therapy and is even more pressing in patients with a history or current use of PUVA or sun exposure.
REFERENCES


